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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| 09/533,466 | 03/23/00 | COLLART | 21416/90042 |

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| EXAMINER | |
|---|---|
| OGIHARA,N | |
| **ART UNIT** | **PAPER NUMBER** |
| 1631 | 7 |

**DATE MAILED:** 10/20/00

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/533,466 | COLLART ET AL. | |
| | Examiner | Art Unit | |
| | Nancy Ogihara | 1631 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

**Status**

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 1-14 is/are pending in the application.

4a) Of the above claim(s) 9-14 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-8 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claims 1-14 are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

**Attachment(s)**

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

## DETAILED ACTION

### *Response to Restriction Requirement*

Applicant's written election without traverse of Group I, claims 1-8, in the paper filed 10/3/00 is acknowledged. Claims 9-14 are withdrawn from further consideration as being drawn to a non-elected invention. Claims 1-8 are pending and under consideration as elected.

### *IDS*

The reference listed as BE, with first author Holbrook does not contain a date of publication as is required. Therefore, the reference has not been considered by the Examiner.

Reference BA, Collart *et al.*, is a duplicate of reference AZ, and has been lined through on the IDS.

### *Sequence Rules*

This application contains sequence disclosures (see for example, Table 2 and Table 7, page 36-37) that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 since no submission of a computer readable form of the sequences has been submitted. Applicants are given the same response time regarding this failure to comply as that set forth in this office action.

### *Claim Objections*

Claim 4 is objected to for containing additional periods (".") within the claim. Periods may not be used elsewhere in the claims except for at the end of the claim and for abbreviations (see MPEP 608.01(m)). Appropriate correction is required.

### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 5-7 are directed to a polypeptide which has the same characteristics as polypeptides found naturally and therefore does not constitute patentable subject matter.

In the absence of the hand of man, naturally occurring products are considered non-statutory subject matter. Diamond v. Chakrabarty, 206 USPQ 193 (1980). Mere purity of naturally occurring products does not necessarily impart patentability. Ex parte Siddiqui 156 USPQ 426 (1966). However, when purity results in new utility, patentability is considered. Merck Co. v. Chase Chemical Co. 273 F. Supp 68 (1967). See also American Wood v. Fiber Disintegrating Co., 90 US 566 (1974); American Fruit Growers v. Rogdex Co. 283 US 1 (1931); Funk Brothers Seed Co. V. Kalo Innoculant Co. 33 US 127 (1948). Filing of evidence of a new utility imparted by the increased purity of the claimed invention and amendment to the claims to recite the essential purity of the claimed products is suggested to obviate this rejection. For example, "An isolated molecule..."

***Claim Rejections - 35 USC § 112***

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ 2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Although the specification discloses the crystal structure of *S. pyogenes* IMPDH, the specification does not teach of a "binding pocket" so that one of skill in the art could predictably identify which residues are encompassed by the term. As set forth in the rejection under 35 U.S.C. 112, second paragraph, it is acknowledged that "binding pocket" is defined as a space where an inhibitor is bound (page 3, lines 28-30 of the specification). However, the metes and bounds of the

term are unclear since there is no specific disclosure of residues that comprise a binding pocket or any criteria for which to judge whether a residue would be included in such a binding pocket. Therefore, one of skill in the art could not be able to predictably identify the binding pocket or the binding pockets from homologous sequences that 60% or more identical. Such a method would require undue experimentation, and therefore, the specification is not enabling for the breadth of the pending claims.

Claim 6 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specifically disclosed crystal of S. pyogenes IMPDH, does not provide evidence to support the claim for homologues comprising less than 100% sequence identity and, therefore, fails to enable the scope of the claim

It is noted that Applicants have claimed a molecule with a percentage sequence identity to a claimed molecule. Absent factual evidence, a percentage sequence identity of less than 100 % is not deemed to reasonably support to one skilled in the art whether the biochemical activity of the claimed subject matter would be the same as that of such a similar known biomolecule. It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change, mutation, or even conservative substitution can destroy the function of the biomolecule in many instances, albeit not in all cases (see Geysen *et al.*, J. of Molecular Recognition, vol. 1, pp. 32-40, 1988). The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, the citation of sequence similarity results in an unpredictable and therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecule of known function and therefore lacks support regarding utility and/or enablement. Several publications document this unpredictability of the relationship between sequence and function, albeit that certain specific sequences may be found to be conserved over biomolecules of related function upon a significant amount of further research. See the following publication that supports this unpredictability as well as noting certain conserved sequences in limited specific cases: Russell *et al.*(Journal of Molecular Biology, Volume 244, pages 332-350, 1994).

Therefore, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with the claim.

Claims 1-8 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 4-8 are vague and indefinite in the recitation of the abbreviated term "IMPDH." The full name of IMPDH should be completely spelled out at its first appearance and not abbreviated. Appropriate correction is required.

Claim 4 fails to correlate obtaining a crystal of IMPDH to the preamble goal of developing lead compounds for an inhibitor of IMPDH. That is, there are no method steps that result in the development of a lead compound. Furthermore, it is unclear whether or not the preamble practice is required for the practice of the actual claim steps.

Claims 5 and 6 are vague and indefinite in the recitation of the term "binding pocket." The metes and bounds of the term are unclear as it is not certain what is meant by "binding pocket." It is acknowledged that "binding pocket" is defined as a space where an inhibitor is bound (page 3, lines 28-30 of the specification). However, it is not certain which residues would be encompassed by such a pocket, i.e. do the residues include those direct contact with the inhibitor, residues in proximity, but not necessarily contacting, those within van der Waals distance, etc...

Claim 7 is vague and indefinite in the recitation of amino acid numbering. The numbering of a sequence is relative to a SEQ ID or a designated sequence, and by itself, does not designate a unique sequence because of the non-uniformity in sequence numbering from one protein to another within a set of related proteins. For example, are the amino acid numbers of claim 7 intended to refer to those of Table 7?

Claim 8 is vague and indefinite in the recitation of the abbreviated term "IMP." The full name of IMP should be completely spelled out at its first appearance and not abbreviated. Appropriate correction is required.

Claim 7 recites a "molecule comprising coordinates." A molecule is a chemical compound, whereas coordinates are numerical locations presumably for the atoms of the claimed molecule. A molecule can be characterized or defined by coordinates, however, it is not certain how a molecule can comprise coordinates.

Claim 8 is vague and indefinite in the recitation of the term "binding site." The metes and bounds of the term are unclear as it is not certain what is meant by "binding site." For example, the term can be interpreted as a ligand binding site, an inhibitor binding site, a co-activator binding site, a

solvent binding pocket or cleft, etc... Furthermore, the it is not certain which residues would be encompassed by such a site, e.g. the residues in direct contact with a ligand, inhibitor, or cofactor, residues in proximity, but not necessarily contacting, etc... Furthermore still, is "binding site" referring to the "binding pocket" of claims 5 and 6?

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-8 are rejected under 35 U.S.C. 102(a) as being anticipated by Zhang *et al.* (Biochemistry, Vol. 38, pp. 4691-4700, 13-April-1999).

Zhang *et al.* disclose the crystal composition, crystallization methods, and the X-ray structure determination of *S. pyogenes* IMPDH (see Materials and Methods section, page 4692-93). The crystallized IMPDH was cloned and expressed in *E.coli* (i.e. a bacterial preparation), however, it should be noted that patentable weight is given to the IMPDH composition, since the distinguishing features of the composition are in the specific sequence, structure, and function of IMPDH and not the bacterial preparation from which it came. The crystals of IMPDH, which included the ligand IMP (see page 4693, left column, 1st full paragraph) were used to record X-ray diffraction data which were subsequently used to generate electron density maps to model the structure of IMPDH (see Figure 2, page 4694). The molecule and molecular complex solved by Zhang *et al.* comprises an IMPDH binding pocket as defined by the coordinates of Table 7 (see Figure 3, page 4695) and comprises the residues as set for in claims 5 and 7. Given the above, Zhang *et al.* meet the limitations of the claims. It should be noted that submission of a Katz type Declaration may be sufficient to obviate this rejection.

Claims 1-6, and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Sintchak *et al.* (IDS document: Cell, vol. 85, pp. 921-930, 1996).

Sintchak *et al.* disclose the crystal composition, crystallization methods, and the X-ray structure determination of chinese hampster IMPDH type II in complex with IMP (see Experimental Procedures, page 928). The crystallized IMPDH was cloned and expressed in E.coli (i.e. a bacterial preparation), however, it should be noted that patentable weight is given to the IMPDH composition, since the distinguishing features of the composition are in the specific sequence, structure, and function of IMPDH and not the cloning vehicle from which it came. The crystals of IMPDH, which included the ligand IMP (see page 921, right column, 2nd full paragraph) were used to record X-ray diffraction data which were subsequently used to generate electron density maps to model the structure of IMPDH (see Phasing, Model Building, and Refinement, page 928). It should be noted that the diffraction patterns obtained by Sintchak *et al.* would be useful for defining molecular structures of similar bacterial IMPDHs through the use of such methods as molecular replacement. The molecule and molecular complex solved by Sintchak *et al.* reads on a molecule comprising a homologue of the *S. pyogenes* IMPDH of the instant invention. Therefore, Sintchak *et al.* meet the limitations of the claims.

Claims 5 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Collart *et al.* (IDS document: Gene, vol. 174, pp. 209-216, 1996).

Collart *et al.* disclose the cloning and purification of IMPDH from *Pyrococcus furiosus* (see title). Collart *et al.* disclose that bacterial and eukaryotic forms of IMPDH are similar in size and show a high degree of amino acid sequence conservation (see page 209, right column). The *Pyrococcus furiosus* IMPDH reads on a molecule comprising a homologue of the *S. pyogenes* IMPDH of the instant invention. Therefore, Collart *et al.* meet the limitations of the claims.

Claims 1-6, and 8 are rejected under 35 U.S.C. 102(e) as being anticipated by Wilson *et al.* (U.S. Patent No. 6,128,582).

Wilson *et al.* disclose the crystal compositions, crystallization methods, and the X-ray structure determination of chinese hampster IMPDH type II (see column 20, lines 40-45). The crystallized

IMPDH was cloned and expressed in E.coli (i.e. a bacterial preparation), however, it should be noted that patentable weight is given to the IMPDH composition, since the distinguishing features of the composition are in the specific sequence, structure, and function of IMPDH and not the cloning vehicle from which it came. The crystals of IMPDH, which included the ligand XMP which Wilson *et al.* disclose as being a form of IMP (see column 5, lines 30-31) were used to record X-ray diffraction data which were subsequently used to generate electron density maps to model the structure of IMPDH (see Figure 4). It should be noted that the diffraction patterns obtained by Wilson *et al.* would be useful for defining molecular structures of bacterial IMPDH through the use of such methods as molecular replacement. The molecule and molecular complex solved by Wilson *et al.* reads on a molecule comprising a homologue of the *S. pyogenes* IMPDH of the instant invention. Therefore, Wilson *et al.* meet the limitations of the claims.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy Ogihara whose telephone number is (703) 308-9363. The examiner can be reached Monday-Friday from 8:30-5:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Michael Woodward can be reached at (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center receptionist, whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1631 by facsimile transmission. Papers should be faxed to Group 1631 via the PTO Fax Center located in Crystal Park I. The faxing of such papers must conform with the notice published in the Official 1Gazette 1096 OG 30 (November 15, 1989). The CMI Fax Center number is (703) 308-4242.

Nancy Ogihara
October 16, 2000

ARDIN H. MARSCHEL
PRIMARY EXAMINER